



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Chapter I

[Docket No. FDA-2012-N-0170]

Modernizing the Regulation of Clinical Trials and Approaches to Good Clinical Practice; Public Hearing; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA) is announcing a 2-day public hearing to obtain input from interested persons on FDA's scope and direction in modernizing the regulations, policies, and practices that apply to the conduct of clinical trials of FDA-regulated products. Clinical trials are a critical source of evidence to inform medical policy and practice, and effective regulatory oversight is needed to ensure that human subjects are protected and resulting clinical trial data are credible and accurate. FDA is aware of concerns within the clinical trial community that certain regulations and policies applicable to the conduct of clinical trials may result in inefficiencies or increased cost and may not facilitate the use of innovative methods and technological advances to improve clinical trial quality. The Agency is involved in an effort to modernize the regulatory framework that governs clinical trials and approaches to good clinical practice (GCP). The purpose of this hearing is to solicit public input from a broad group of stakeholders on the scope and direction of this effort, including encouraging the use of innovative models that may enhance the effectiveness and efficiency of the clinical trial enterprise.

Date and Time: The public hearing will be held on April 23 and 24, 2012, from 8:30 a.m. to 4:30 p.m. Individuals who wish to attend or present at the public hearing must register on or before close of business on April 2, 2012. To register for the public hearing, email your registration information to ClinTrialPublicMt@fda.hhs.gov. Section IV of this document provides attendance and registration information. Electronic or written comments will be accepted after the public hearing until May 31, 2012.

Addresses: The public hearing will be held at FDA's White Oak Campus, 10903 New Hampshire Ave., Bldg. 31, rm. 1503, Silver Spring, MD 20993-0002.

Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify comments with the corresponding docket number found in brackets in the heading of this document.

Transcripts of the public hearing will be available for review at the Division of Dockets Management and on the Internet at <http://www.regulations.gov> approximately 30 days after the public hearing (see section VII of this document).

A live webcast of this public hearing can be viewed at the following Web address on the days of the public hearing: <http://www.fda.gov/Drugs/NewsEvents/ucm284118.htm>. A video record of the public hearing will be available at the same Web address for 1 year.

FOR FURTHER INFORMATION CONTACT:

Jennifer Hymiller,
Food and Drug Administration,
Center for Drug Evaluation and Research,
10903 New Hampshire Ave.,

Bldg. 51, rm. 6333,
Silver Spring, MD 20993-0002,
301-796-2147, FAX: 301-847-3529,
Email: ClinTrialPublicMt@fda.hhs.gov

SUPPLEMENTARY INFORMATION:

I. Background

Clinical trials that yield reliable data are critical to FDA's mission to ensure that drugs, biologics, and medical devices are safe and effective. The regulations that govern the conduct of clinical trials and the protection of human subjects have been in existence for more than 25 years. In the intervening years, there have been dramatic changes in the clinical trial enterprise, including increased size and complexity of clinical trials, increases in the number of clinical trials performed globally, greater use of contract research organizations (CROs), participation of vulnerable populations, and numerous scientific and technological advances. Given these changes and the evolution of the clinical trial enterprise, FDA is evaluating its regulatory approach to clinical trial oversight to ensure that it meets the regulatory objectives of ensuring human subject protection and the quality and integrity of data supporting regulatory decision-making, without being unnecessarily burdensome or unduly impeding implementation of innovative approaches. FDA has already taken a number of steps to improve and modernize its regulations, policies, and practices to ensure they provide for optimal clinical trial quality, data integrity, human subject protection, and flexibility.

In 2004, FDA introduced the Critical Path Initiative (CPI),¹ intended to transform the way medical products are developed, evaluated, and manufactured. One of the CPI's key areas

¹ For more information on FDA's Critical Path Initiative, see <http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/default.htm>.

of focus is modernizing clinical trial sciences to make trials safer and more efficient. As part of this larger initiative, FDA launched two initiatives to specifically address human subject protection, data integrity, and clinical trial quality and efficiency.

In 2006, FDA launched the Human Subject Protection and Bioresearch Monitoring Initiative² aimed at modernizing and strengthening FDA's oversight and protection of human subjects and the integrity of data in clinical trials. FDA's Office of Good Clinical Practice in the Office of the Commissioner is leading this effort. FDA also established a Human Subject Protection and Bioresearch Monitoring Council that manages and sets FDA policy on bioresearch monitoring, GCP, and human subject protection.

In 2007, FDA and Duke University formed the Clinical Trials Transformation Initiative (CTTI),³ a public-private partnership with the goal of improving the quality and efficiency of clinical trials. CTTI has been involved in a range of projects, including projects to identify best practices for monitoring and designing quality into clinical trials, improve serious adverse event reporting to investigators, and gather best practices for premarket safety surveillance.

In 2011, FDA published a Federal Register notice requesting comment on the development of a plan for the retrospective review of existing FDA regulations⁴ in accordance with Executive Order 13563, "Improving Regulation and Regulatory Review." As part of this plan, FDA is conducting a review of existing regulations to determine which, if any, of its rules are outmoded, ineffective, insufficient or excessively burdensome and may be good candidates to

² For more information on FDA's Human Subject Protection and Bioresearch Monitoring Initiative, see <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm226306.htm>.

³ For more information on the Clinical Trials Transformation Initiative, see <https://www.trialstransformation.org/>.

⁴ 76 FR 23520; April 27, 2011.

be modified, streamlined, expanded or repealed. The Agency is also evaluating its framework for periodically analyzing existing rules.⁵

Over the past few years, FDA has issued a number of regulations and guidance documents related to clinical trial conduct. The following regulations and guidances are highlighted below to exemplify the direction and scope of FDA's effort to modernize the regulations, policies, and practices that apply to the conduct of clinical trials. The CPI, Human Subject Protection and Bioresearch Monitoring Initiative, and CTTI have helped inform these regulations and guidances:

1. Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies--Final Rule, published September 29, 2010 (75 FR 59935);

2. Investigator Responsibilities--Protecting the Rights, Safety, and Welfare of Study Subjects--Final Guidance, published October 26, 2009 (74 FR 55052);

3. Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring--Draft Guidance, published August 29, 2011 (76 FR 53683);

4. Electronic Source Documentation in Clinical Investigations--Draft Guidance, published January 7, 2011 (76 FR 1173);

5. Adverse Event Reporting to IRBs--Improving Human Subject Protection--Final Guidance, published January 15, 2009 (74 FR 2599);

6. Exception from Informed Consent Requirements for Emergency Research--Final Guidance, published April 4, 2011 (76 FR 18558);

The collaborative effort with CTTI also identified Quality Risk Management (QRM) principles and Quality by Design (QbD) as models that, with adaptations, could contribute to

⁵ 76 FR 3821.

improved data quality and integrity in clinical trials. QRM is a systematic process to identify, assess, control, communicate, and review the risks associated with a process or activity. QbD, a risk-based, quality approach that has been successful in the manufacturing arena, emphasizes building quality into a process from the beginning. Applied to clinical trials, this approach would prospectively define factors most critical to trial quality and data integrity (e.g., proper randomization, effective blinding to ensure unbiased ascertainment and analysis of study outcomes) and prospectively identify risks critical to those factors. The sponsor would then design the protocol, oversight and monitoring mechanisms, as well as data management, archiving, and analysis processes to eliminate or mitigate those risks.

FDA has also taken steps to improve its clinical trial inspection processes and coordinate inspection processes globally. Ongoing efforts are aimed at developing new approaches for selecting clinical investigator sites for inspection and for improving the warning letter process. FDA is also involved in a Good Clinical Practice Initiative⁶ with the European Medicines Agency (EMA), in which FDA and the EMA have shared information on applications, collaborated on joint and observational inspections, participated in bilateral training, and kept each other informed of GCP-related legislation, regulatory guidance, and related documents. These steps have facilitated improvements in FDA's inspection coverage and decision-making processes.

In various forums, FDA has been told that certain regulations and compliance practices may result in inefficiencies or may not facilitate the use of innovative methods to improve clinical trial quality or the use of technological advances (e.g., use of the Internet to gather data, conduct certain types of research, obtain informed consent). FDA has also heard from clinical

⁶ For more information on the EMA-FDA Good Clinical Practice Initiative, see <http://www.fda.gov/downloads/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanUnion/EuropeanCommission/UCM266259.pdf>.

trial sponsors and CROs that sponsors and CROs are reluctant to change their processes related to clinical trial oversight and management because of uncertainty about whether new processes would be in compliance with applicable regulations. FDA recognizes that it must effectively leverage its available resources and take additional steps to strategically evolve and modernize its regulatory approach to the conduct of clinical trials. FDA is striving to align regulatory processes to meet the needs of its many stakeholders, including those who design and conduct trials, those who participate in trials, and those who depend on the results of those trials to make informed health care decisions.

II. Purpose of Hearing

The purpose of this public hearing is to obtain input from clinical trial sponsors, CROs, clinical investigators, academic institutions, institutional review boards (IRBs), professional societies, trade organizations, patient and consumer groups, and other interested parties on the scope and direction of FDA's future efforts to evolve and modernize its regulatory approach to the conduct and oversight of clinical trials. FDA's primary focus is on good clinical practice, including clinical protocol design to ensure the reliability of data, safety surveillance and reporting, quality control processes (e.g., monitoring and training), quality assurance (e.g., auditing), and any other processes directed at ensuring trial quality, data integrity, or human subject protection. FDA is interested in ways (e.g., workshops, strategic alliances) to foster implementation of innovative methods to ensure human subject protection and data quality and integrity, including risk-based approaches in the design, oversight, and conduct of clinical investigations. FDA is seeking feedback on specific GCP regulations, policies, and practices that may need clarification or revision to facilitate advances in the ways that clinical trials are conducted, remove impediments to the use of innovative approaches, or otherwise improve the

conduct of clinical trials. FDA also welcomes comments on additional issues that will help the Agency modernize its oversight and improve the quality and efficiency of clinical trials.

III. Issues for Discussion

In addition to the general information requests in section II of this document, FDA is interested in obtaining information and public comment on the following specific issues.

1. Increasing clinical trial complexity (e.g., participation of vulnerable populations, increased frequency of outsourcing) and globalization are posing challenges for sponsors, clinical investigators, IRBs, patients, and FDA. FDA has been involved in a number of efforts to ensure that the Agency's GCP regulations, policies, and practices are optimal for ensuring clinical trial quality, data integrity, and human subject protection while providing flexibility to conduct trials in the 21st century.

a. What additional efforts should FDA pursue to modernize the Agency's GCP regulations, policies, and practices? For example, are there specific FDA regulations, guidances, or practices (e.g., compliance programs) that should be a high priority for clarification or revision? Are there other steps (e.g., pilot projects, strategic alliances) that would help ensure clinical trial quality and subject safety, provide flexibility, or improve the efficiency of the clinical trial process? For each of the suggested efforts, specifically identify the reasons that the current approach is not optimal, how the suggested effort would ensure clinical trial quality, subject safety, and/or improve the efficiency of the clinical trial process, and what the preferred priority of the efforts should be.

b. What efforts could FDA consider that could help mitigate some of the challenges resulting from increased clinical trial complexity and globalization? For each of the suggested efforts, specifically identify how the effort could help mitigate these challenges.

2. FDA is interested in fostering the use of innovative methods and models, including QRM principles and QbD, as well as the use of technological advances (e.g., use of the Internet to gather data, conduct certain types of research, obtain informed consent). The Agency seeks comments on how the use of innovative methods, models, and technological advances could contribute to data integrity, clinical trial quality, and the safety of human subjects, as well as streamline the conduct of clinical trials.

a. What are some innovative methods or models that facilitate building quality into the conduct of trials (e.g., by identifying, preventing, or minimizing errors that have the potential to compromise human subject safety and data integrity)? FDA requests feedback on experiences with implementing such methods or models (e.g., lessons learned), as well as data supporting the use of any suggested methods or models.

b. FDA recognizes that the clinical trial process involves various stakeholders (e.g., sponsors, CROs, IRBs, investigators, patients) with different roles and responsibilities in ensuring human subject protection and generating valid study data. What are the specific stakeholder challenges presented by FDA's GCP regulations, policies, and/or practices to building quality into the clinical trial process (e.g., for a study that is conducted and overseen by multiple entities)?

c. What are some ways in which FDA could encourage adoption of these methods and models? For example, how can FDA support effective communication and coordination among all entities involved in the conduct of a trial to ensure a focus on the protection of human subjects and quality across the clinical trial process?

d. How should FDA focus its efforts in GCP regulations, policies, or practices to facilitate the use of technological advances, while maintaining the protection of research participants and the quality and integrity of data supporting regulatory decision-making?

IV. Attendance and Registration

The FDA Conference Center at the White Oak location is a Federal facility with security procedures and limited seating. Attendance is free and will be on a first-come, first-serve basis. Individuals who wish to attend the public hearing must register by sending an email to ClinTrialPublicMt@fda.hhs.gov on or before April 2, 2012, and provide complete contact information, including: Name, title, affiliation, address, email, and phone number. Those without email access may register by contacting Jennifer Hymiller (see FOR FURTHER INFORMATION CONTACT). Because seating is limited, FDA may limit the numbers of participants from each organization. Registrants will receive confirmation once they have been accepted for participation in the hearing. Onsite registration on the day of the hearing will be based on space availability on the day of the event starting at 7:30 a.m. If registration reaches maximum capacity, FDA will post a notice closing the meeting registration for the hearing at <http://www.fda.gov/Drugs/NewsEvents/ucm284118.htm>.

Individuals who wish to present at the public hearing must register on or before April 2, 2012, through the email ClinTrialPublicMt@fda.hhs.gov, and state this intention on their notice of participation. You must provide complete contact information, including: Name, title, affiliation, address, email, and phone number. FDA has included questions for comment in section III of this document. You should identify the topic or section and the number of each question you wish to address in your presentation, so that FDA can consider that in organizing

the presentations. Individuals and organizations with common interests should consolidate or coordinate their presentations and request time for a joint presentation. FDA will do its best to accommodate requests to speak and will determine the amount of time allotted for each oral presentation, and the approximate time that each oral presentation is scheduled to begin. FDA will notify registered presenters of their scheduled times, and make available a draft agenda on <http://www.fda.gov/Drugs/NewsEvents/ucm284118.htm> approximately 2 weeks before the public hearing. Once FDA notifies registered presenters of their scheduled times, presenters should submit to electronic copy of their presentation to ClinTrialPublicMt@fda.hhs.gov on or before April 16, 2012.

If you need special accommodations because of disability, please contact Jennifer Hymiller (see FOR FURTHER INFORMATION CONTACT) at least 7 days before the meeting.

A live webcast of this public hearing can be viewed at the following Web address on the days of the public hearing: <http://www.fda.gov/Drugs/NewsEvents/ucm284118.htm>. A video record of the public hearing will be available at the same Web address for 1 year.

V. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with part 15 (21 CFR part 15). The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner, the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health.

Under § 15.30(f), the hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation. Public

hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (part 10, subpart C (21 CFR part 10, subpart C)). Under § 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. The hearing will be transcribed as stipulated in § 15.30(b) (see section VII of this document). To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

VI. Request for Comments

Regardless of attendance at the public hearing, interested persons may submit either electronic or written comments to the Division of Dockets Management (see ADDRESSES). It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

VII. Transcripts

Transcripts of the public hearing will be available for review at the Division of Dockets Management (see ADDRESSES) and on the Internet at <http://www.regulations.gov> approximately 30 days after the public hearing. A transcript will also be made available in either hard copy or on CD-ROM, upon submission of a Freedom of Information request. Written requests are to be sent to the Division of Freedom of Information (ELEM-1029), Food and Drug Administration, 12420 Parklawn Dr., Element Bldg., Rockville, MD 20857

Dated: March 1, 2012.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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